REMARKS

Status Summary

The amendment filed on May 12, 2004, was entered. Claims 61-67 were added, and claims 56-67 were examined. Claims 56-60 remain rejected and new claims 61-67 are also rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 5,776,456 to Anderson et al. (Anderson) in view of U.S. 6,042,826 to Caligiuri et al. (Caligiuri), and further in view of DeAngelis (1998) *J Neurooncology* 38:245-252 (DeAngelis). Claims 56-67 are also rejected based on non-statutory obviousness-type double patenting as allegedly unpatentable over claim 1 in U.S. Patent No. 5,776,456 to Anderson et al. (Anderson).

Claim 56 is amended. Claim 61 is canceled. Reconsideration in view of the claim amendments and following remarks is respectfully requested.

Rejection of Claims Under 35 U.S.C. § 103(a)

Claims 56-60 remain rejected and new claims 61-67 are also rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 5,776,456 to Anderson et al. (Anderson) in view of U.S. 6,042,826 to Caligiuri et al. (Caligiuri), and further in view of DeAngelis (1998) *J Neurooncology* 38:245-252 (DeAngelis). Official action, pages 2-4. This rejection is also respectfully traversed.

The examiner bears the burden of presenting a *prima facie* case for obviousness, which requires: (1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) the teaching or suggestion of all the claim limitations of the applicant's invention in the combined prior art references; and (3) a reasonable expectation of success. MPEP § 2143. Applicant responds that the examiner has failed to meet this burden given the lack of a reasonable chance of success in practicing the claimed invention.

Where the cited documents do not expressly suggest the claimed invention, the examiner is required to show how and why the applicants would have been motivated to combine the references in the manner combined by the examiner. Although the motivation to combine prior art does not have to be expressly stated in the references themselves, "the examiner must present a convincing line of reasoning" for a proper conclusion that an invention is obvious in view of prior art. *See In re Keller*, 642 F.2d 413, 208 USPQ 871

(CCPA 1981). *See also, Ex parte Clapp,* 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). Motivation relies on a reasonable expectation of success.

In contrast to the examiner's assertion, the cited documents do not describe, suggest, or motivate methods for treating a central nervous system (CNS) lymphoma by administering an anti-CD20 antibody such that levels of the anti-CD20 antibody are greater in cerebrospinal fluid (CSF) than in serum. Applicants further submit that, the Caligiuri reference, which describes administration of anti-human Fas monoclonal antibodies, does not enable administration of anti-CD20 antibodies as now claimed. Thus, at the time of filing the instant application, a skilled artisan would not have had a reasonable chance of success in practicing the claimed invention.

Anderson describes methods for treatment of B cell lymphoma via administration of anti-CD20 antibodies. The examiner notes that Anderson does not teach treatment of CNS lymphomas, as now claimed. The examiner concludes that it would have been *prima facie* obvious to modify the methods of Anderson to "include B-cell lymphomas of the central nervous system because such lymphomas merely represent species of the broadly claimed genus of B-cell lymphomas." First official action (paper no. 7), pages 10-12.

The examiner relies on Caligiuri as teaching that primary CNS lymphomas involve the meninges, and on DeAngelis as teaching that lymphomas are a common cause of leptomeningeal metastasis. Based thereon, the examiner concludes that one of ordinary skill in the art would reasonably expect that a subpopulation of patients with CNS lymphoma would also exhibit leptomeningeal lymphoma. Official action, pages 3-5. The examiner also relies on Caligiuri and DeAngelis as teaching combination of immunotherapy with chemotherapy, as in claims 4, 53, and 58. Official action, pages 4-5, bridging paragraph.

The examiner has rejected applicants' arguments that, as of the filing date of the application, methods for achieving the claimed distribution of administered antibodies was not routine. In response to the previously filed amendment, it appears that the examiner maintains the rejection on the basis that "the broad scope of the claims are not limited to any particular route of administration." Official action, page 3. The examiner further states that Caliguiri suggests intrathecal and intraventricular routes of administration of antibodies. In response to applicants' arguments that known intrathecal administration did not predictably result in elevated levels of administered antibodies in cerebrospinal fluid, the examiner contends that the unpredictability of intrathecal administration as described by Cokgor and by

Blaney is not on point as these studies describe intrathecal administration of chemotherapeutics. Official action, pages 3-4.

Claim 56 is amended herein to specify that the anti-CD20 antibody is administered intrathecally or intraventricularly. Support for the amendment is found in previously presented claim 61, now canceled, at page 66, lines 4-5, and at page 67, lines 14-15, of the originally filed specification.

The Anderson, Caligiuri, and DeAngelis, whether considered alone or in combination, do not teach, suggest, or motivate intrathecal administration of anti-CD20 antibodies as now claimed. Although the examiner contends that Caligiuri suggests intrathecal administration of antibodies, applicants submit that this suggestion is limited to intrathecal administration of anti-human Fas monoclonal antibodies. The examiner refers to col. 15, line 12, of Caligiuri, wherein it is claimed that "the at least one chemotherapeutic agent is administered intrathecally or intrlesionally." Official action, page 3. Applicants note that the cited text refers to administration of chemotherapeutic agents, not antibodies as presently claimed. Applicants also note, however, that claim 7 of the Caligiuri patent is directed to intrathecal or intralesional administration of a Fas-cross-linking composition, including an anti-human Fas antibody (col. 14, lines 40-47). All references to intrathecal administration, as described in the Caliguiri patent, specify administration of an anti-human Fas antibody. The Caliguiri patent does not generally suggest intrathecal administration or any antibody and does not suggest administration of an anti-CD20 antibody as now claimed.

In addition, applicants submit that one skilled in the art would not be motivated to replace the anti-Fas antibody in the methods of Caliguiri with an anti-CD20 antibody to arrive at the presently claimed invention. Specifically, such motivation would not have existed as of the filing date of the instant application because success in performing such method did not reasonably exist. Despite that the Caliguiri reference suggests administration of an anti-Fas antibody, this suggestion does not enable performance of intrathecal administration of any antibody by the proposed substitution.

A reference is enabling if the public was in possession of the claimed invention. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." *In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985).

Applicants note that the Caliguiri patent does not include any experimental results showing that anti-Fas antibodies can be administered to a subject via intrathecal injection to thereby achieve antibody levels that are higher in cerebrospinal fluid than in serum, as presently claimed. Given the absence of any evidence demonstrating successful performance of intrathecal antibody administration, a skilled artisan would not have concluded, based on the disclosure of Caliguiri, that the presently claimed invention could be achieved with any reasonable chance of success.

In addition, although the examiner dismisses the Cokgor and Blaney references as not pertinent to antibody administration methods, the examiner has not cited any reference that demonstrates successful intrathecal administration of antibodies. Applicants submit that these references are material as to whether such administration methods could have been successfully performed, despite what type of composition is being administered. The Cokgor and Blaney references support the unpredictability of intrathecal administration methods generally, which includes administration of antibodies.

As argued previously, intrathecal administration techniques do not predictably result in drug levels in cerebrospinal fluid that are higher than serum levels. As described by Cokgor, intralumbar administration (one type of intrathecal administration) is associated with limited drug distribution at the site of injection. *See* Cokgor et al. (2002) *J Neuro-Oncol* 60:79-88, page 81, col. 1, ¶ 4 (copy previously submitted). In addition, the administered antibodies may be metabolized or eliminated from the intrathecal space, which would defeat achievement of levels of antibody that are higher in cerebrospinal fluid than in serum. Other factors that compromise achievement of elevated levels of antibody in cerebrospinal fluid include the volume of cerebrospinal fluid and the presence of leptomeningeal disease. *See e.g.*, Blaney et al. (2000) *Med Oncol* 17:151-162, pages 156-7, bridging paragraph (copy previously submitted).

Applicants also submit a copy of Hanssens et al. (1998) *J Neurooncol* 38(2-3):145-150 (Hanssens), which states that, despite theoretical advantages, "[intrathecal administration of radiolabeled antibodies] is still under investigation and subject to some limitations and toxicities." (abstract). Even after the priority date of the instant application, Ruggiero et al. report that "[m]onoclonal antibodies, reactive with tumour-associated antigens, can be used as delivery systems for chemotherapeutic agents and radionuclides. However, the development of this new approach is currently under evaluation in larger clinical studies.

Neurological adverse effects may be expected with intrathecal chemotherapy . . . . " Ruggiero et al. (2001) *Paediatr Drugs* 3(4):237-246 (Ruggiero) (abstract). Development of adverse effects of intrathecal administration, as described by Ruggiero, is contrary to administration of a therapeutically effective amount, as now claimed. The Hanssens and Ruggiero references further support that intrathecal administration of antibodies was unpredictable as of the filing date of the instant application.

Thus, prior to the disclosure of the instant application, one could not have reasonably predicted that elevated levels of anti-CD20 antibody in cerebrospinal fluid could be achieved. In the absence of a reasonable chance of success in practicing the invention, the claims are not *prima facie* obvious.

Based on the foregoing arguments, applicant believes that claims 56-60 fully comply with the requirements of 35 U.S.C. § 103(a) and request that the rejection of claims 56-60 based on Anderson, Caligiuri, and DeAngelis be withdrawn.

Rejection of Claims Based on Non-Statutory Obviousness-Type Double Patenting

Claims 56-60 are rejected based on non-statutory obviousness-type double patenting as allegedly unpatentable over claim 1 in U.S. Patent No. 5,776,456 to Anderson et al. (Anderson). Official action, page 5, second paragraph, through page 7. This rejection is respectfully traversed.

Based on the arguments set forth above in response to the rejection of claims under 35 U.S.C. § 103(a), which are incorporated herein, applicant believes that the methods of the present disclosure are non-obvious in view of Anderson. As such, applicant also requests that the obviousness-type double patenting rejection be withdrawn.

Conclusion

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,
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